CROSS-SECTIONAL ASSOCIATIONS BETWEEN MOVEMENT BEHAVIOURS, OBESITY, AND METABOLIC SYNDROME IN AN OUT-PATIENT POPULATION WITH SUSPECTED CORONARY MICROVASCULAR DYSFUNCTION

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Abstract

Background: Coronary Microvascular Dysfunction (CMVD), affects the smaller vasculature and is difficult to diagnose without invasive tests. Little is known about the relationship between movement behaviours and CMVD, which may offer insight for primary prevention and early management. **Objective**: Examine and compare patterns of obesity, metabolic health, and movement behaviors amongst patients with CMVD and epicardial disease. **Methods**: The relationship between metabolic health, movement behaviors, and CMVD were estimated by logistic regression (unadjusted and adjusted for confounders). **Results**: Sleep quality and quantity were significantly worse in those with suspected coronary microvascular dysfunction. Physical activity was not significantly different between referral groups. Interestingly, obese-CMVD patients were 31.7% more likely to have suspected CMVD compared to their normal weight counterparts. **Conclusions**: Despite a relatively high prevalence of inactivity, sleep disturbance, MetS, and general and abdominal obesity, patterns of lifestyle factors did not materially differ between cases of suspected CMVD and epicardial disease.

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1.0 Introduction

Cardiovascular disease (CVD) is one of the largest causes of death worldwide, responsible for approximately 30% of deaths globally (1). Within Canada, approximately one-third of all deaths are attributable to CVD, making it the second leading cause of death within the nation (1). It is no surprise that heart disease imposes major financial costs within the nation, with CVD costing the Canadian government $21 billion per year in direct and indirect costs (1). Coronary artery disease (CAD), one of the many sub-groups of CVD, accounts for 29% of all deaths (2), and can be further refined into two larger categories based on the type of coronary vasculature at risk. Well-known macrovascular issues often include the presence of blockages in large vessels surrounding the heart, secondary to atherosclerosis, known as obstructive CAD (3), or which may be referred to as traditional epicardial CAD in this study. A commonly accepted cut-off for obstructive CAD consists of stenosis, or narrowing of the artery, of 70% in a main coronary artery (3). Such macrovascular concerns may also include mechanical problems, such as coronary artery spasms and myocardial bridging. Comparatively, microvascular-related issues been shown to increase coronary resistance in the smaller vessels around the heart, with the potential of progressing into future cardiac complications (3).

Currently, several competing theories surrounding the pathophysiology of coronary microvascular dysfunction (CMVD) exist. Some studies have hypothesized that the cause of CMVD can be attributed to a reduced nitric oxide release, ultimately impairing endothelium-dependent vasodilation (4). Moreover, a limited number of studies have suggested that CMVD is heavily influenced by endothelial progenitor cell abnormalities (4). The most common theory regarding the pathophysiology of microvascular dysfunction is an increase in resistance and obstructed blood circulation within the arterioles surrounding the heart (5). Microvascular

dysfunction is especially concerning as it is often undetected in patients, particularly women, with symptoms of angina who otherwise present as "normal" upon coronary angiography (6) and are often quickly discharged and told that they are not at imminent risk of a cardiac event. However, upon further follow-up, up to 65% of these same patients have evidence of microvascular dysfunction, a condition referred to as Functional Coronary Artery Disease (Functional CAD) (6).

Despite the many non-modifiable risk factors, approximately 80% of CAD-related events are a result of lifestyle-related factors (7). These modifiable behaviours have also been shown to play a large role in the development of functional CAD (8), with factors ranging from poor quality and duration of sleep, increased mental stress, and a sedentary lifestyle. It remains unclear whether these lifestyle factors are a pre-cursor to microvascular dysfunction or whether the presence of these risk factors brings rise to new comorbidities, such as metabolic syndrome (MetS), as they are all heavily interconnected. It is for this reason that it is necessary to work towards identifying the contributing factors in order to help screen and prevent disease progression in patients at greatest risk of CMVD.

2.0 Literature Review

2.1 Metabolic Syndrome and Coronary Microvascular Dysfunction

As defined above, MetS consists of a combination of metabolic abnormalities that play a significant role in the progression of both cardiovascular diseases and type 2 diabetes mellitus (9). According to the National Cholesterol Education Program - Third Adult Treatment Panel (modified NCEP ATP III) (10), the diagnostic criteria for MetS requires the presence of 3 out of 5 of the following characteristics: increased waist circumference (>102 cm [>40 in] for men, >88 cm [>35 in] for women), elevated triglycerides (≥150mg/dl), low HDL cholesterol (<40 mg/dl in men, <50 mg/dl in women), hypertension (≥130/ ≥ 85 mmHg), and impaired fasting glucose (≥100 mg/ dl) (11). The severity of the condition has not gone unnoticed, as individuals with MetS have a two-fold elevated risk of all-cause mortality, and a three-fold elevated risk of diabetes, as compared to those without MetS (12) ultimately marking MetS as an early warning sign for impending health risk.

Cross-sectional studies have shown that almost one third of the Canadian population has MetS. Although the pathways linking the various components of MetS are not fully understood, an increase in intima-media thickness, arterial stiffness, systemic inflammation, and other factors have been implicated in the onset of hypertension, serving as a domino effect for many of these related chronic conditions (13, 14, 11). As the components of MetS are also considered classic CAD risk factors, the risk of developing cardiovascular and coronary diseases increases significantly with MetS (14). For example, in a study of 811 patients with and without MetS, Espinola-Klein et al. (15), MetS was found to be an independent risk factor for cardiovascular events (15). Similarly, in a study by Kazlauskienė et al (2015), more than half of all patients with acute coronary syndrome were also diagnosed with MetS (16). One previous study has examined

the co-occurrence of MetS and CMVD in a clinical setting (17), results of which suggest that microcirculatory dysfunction may be strongly associated with MetS. While insulin resistance and hypertension may be particularly affected, additional work is necessary to assist in identifying CMVD patients who might be missed through traditional measures of coronary dysfunction.

2.2 Microvascular Disease in Women

Although heart disease has always been thought of as a "man's disease," recent research has shown that women are more susceptible to developing microvascular disorders when compared to men (18). Specifically, approximately 60% to 70% of women who undergo coronary angiography are found to have functional CAD as opposed to only 30% of men. To expand on this, women are more likely to have "normal" coronary arteries upon coronary angiograph (19) when compared to men, as more than 50% of women who undergo cardiac catheterization as a result of chest pain display non-obstructive coronary arteries, or "smooth lesions" (20). In a study by Humphries et al. (2008), re-hospitalization within 180 days for acute coronary syndrome or chest pain in patients with "normal" angiography was four-fold higher for women as compared to men (21). This high rate of recurrence is echoed in results of the Women's Ischemia Syndrome Evaluation (WISE) study wherein more than 40% of women with non-obstructive coronary disease and evidence of myocardial ischemia were re-hospitalized for chest pain on multiple occasions, and 30% of these women were re-admitted for an additional coronary angiogram within 5 years of their initial visit (20).

Despite the seemingly normal looking arteries, one study observed a 20% mortality rate in patients with poor coronary flow reserve as opposed to only 7% of those with normal coronary flow reserve (22). Additionally, microvascular dysfunction has been shown to lead to traditional obstructive CAD (23). In one study, 30% of patients with suspected microvascular dysfunction

developed obstructive CAD within 10 years of initial assessment (23). As coronary heart disease is the leading cause of death amongst women (24) in the U.S. - with approximately two-thirds of women having no previous symptoms (25) - these findings suggest that appropriate screening tools for CMVD is imperative. Women are not only more likely to develop CMVD but are also more at risk at being clinically overlooked. Studies have shown that women are less likely to receive extensive cardiac investigation of symptoms (26) and are less likely to receive treatment for thrombolysis (27) angioplasty or cardiac surgery (28) upon consultation. It is for this reason that females are considered to be an "under-represented" population when compared to men, as their symptoms are most often depicted as benign and low-risk.

2.3 *Relationship between BMI and Microvascular Dysfunction*

It is well-understood that in most traditional CAD cases, as body mass index increases, so does one's risk of developing cardiac abnormalities. This is often the result of atherosclerosis (29) or the build-up of plaque on vessel walls, which ultimately impedes coronary flow. However, a recent study by Van Der Heijden et al. (2017) also looked at the influence of obesity in patients with microvascular endothelial dysfunction and compared the results to traditional risk factors, such as diabetes, smoking, hypertension, etc., in patients with suspected CAD (30). It was found that in the 108 patients examined, that an increased body mass was associated with reduced endothelial function upon adjustments for existing comorbidities (30). It has been hypothesized that higher body mass is detrimental to endothelial function as a result of increased adipose-related secretions, and an imbalance in healthy perivascular adipose tissue (PVAT) from non-obese patients (31); all of which are essential to maintaining healthy endothelial function. Another recent and larger study by Bajaj et al. (2018) examined 827 patients without traditional

obstructive CAD with those with symptoms of coronary microvascular dysfunction, defined as having impaired coronary flow reserve (CFR). Results of this study demonstrated an inverted J-shape relationship between BMI and CFR wherein at low levels of BMI, CFR decreased, and amongst those at higher BMI, CFR was increased (32).

2.4 Sleep Duration and Quality on Microvascular Dysfunction

Although it is well-established that one's overall quality of life is often compromised following a significant cardiac event (33), the reverse may also be true (34). Common sleep disorders affecting both sleep quality and duration, such as sleep apnea and obstructive sleep disorder, have been shown to be independently associated with atherosclerosis and heart remodeling (35). However, it is difficult to discern the relative importance of sleep quality and quantity in the development of cardiovascular diseases, as sleep duration may increase as a result of poor-quality sleep, particularly in patients with pre-existing medical conditions (36).

A number of studies to date have investigated the relationship between sleep dysfunction and cardiovascular health. For example, in a study of the effects of sleep duration and quality over a span of 10-15 years, it was observed that short sleepers with poor sleep quality had a 63% higher risk of CVD and a 79% higher risk of CHD incidence in comparison to normal sleepers with good sleep quality (37). In addition to this, a prospective study aimed at investigating the relationship between obstructive sleep apnea (OSA) and CAD also demonstrated that the treatment of OSA was associated with a decrease in the number of cardiac events occurring in patients with both chronic conditions, as well as a decrease in the time to a cardiac event (38). Many patients with OSA have also been found to have hypertension, which has been associated to a number of microvascular conditions, such as perivascular fibrosis, a reduction in the number

of capillaries per gram of muscle tissue, reduced vascular lumen, as well as coronary microvascular anomalies (38). Finally, the Wisconsin Sleep Cohort Study, a recent longitudinal analysis, found similar results upon examining over a thousand individuals with sleep-disordered breathing (SDB). Over the span of 24 years it was observed that participants with severely untreated SDB were 2.6 times more likely to develop CHD or heart failure, even after adjustment for confounders (39).

Beyond the studies described above, the relationship between more general patterns of sleep and microvascular dysfunction is an area of emerging research interest, given that impaired microvascular function is often a pre-cursor in the development of cardiovascular disease (40). Indeed, poor sleep patterns are believed to impact microvasculature as a result of systemic low-grade inflammation (41). In a study of healthy adults in Amsterdam (42), despite the finding of no significant relationship between sleep quality on microvascular function in women, men with poor sleep patterns were shown to have decreased capillary recruitment, and ultimately, reduced microvascular function. Findings such as these have led some researchers (43) to theorize that certain sleep disorders, such as SDB, may be the driving force behind the development of endothelial dysfunction, systemic inflammation, and insulin resistance as a result of chronic nocturnal hypoxemia during sleep (43). Despite the uncertainty surrounding the etiology of microvascular dysfunction, it remains clear that both sleep duration and quality are important risk factors to consider and further examine in the development of CMVD.

2.5 Physical Activity, Sitting Time and Microvascular Dysfunction

Not unlike most chronic conditions, physical inactivity has been shown to have significant effects on the development of both traditional macrovascular heart disease and functional CAD (44). While research on lifestyle related risk factors and CMVD is still in its

infancy, considerable evidence now supports current physical activity guidelines, stating that engaging in 150 minutes of moderate-to-vigorous physical activity per week or more is associated with a graded reduction in mortality and major cardiovascular diseases (45, 46). While there are a number of mechanisms at play, activating large muscle groups by means of physical activity can increase peak aerobic capacity, which is itself inversely related to all-cause mortality in patients with CAD (47). Although the benefits of physical activity are well established and highly promoted, research now suggests that maintaining an active lifestyle is just as beneficial as in engaging in intentional physical activity (48). More specifically, Kulinski et al. (2014) demonstrated that sitting for 6-7 hours can actually negate the effects of one-hour of moderate level exercise per day. Although it remains unclear which of the two is ideal for improving heart (and specifically microvascular) health, it remains evident that both engaging in regular exercise or maintaining an active lifestyle is necessary to reduce one's risk of developing future cardiac events. The systemic consequences of regular activity include an increase in the body's demand for myocardial oxygen, thus increasing coronary blood flow, and with continued training, cardiovascular adaptation can reduce the risk of myocardial infarctions and symptoms of angina (49). This is especially important in aiding in the prevention of microvascular dysfunction, as many patients with microvascular disorders display patterns of significant arterial stenosis, a consequence of limited coronary blood flow (49). As discovered by Hanna et al. (2014), exercise training was found to reduce resistance vessel hypertrophic remodeling and vessel stiffness, while helping to re-establish myogenic responsiveness and improving epicardial microcirculation (50). This suggests that chronic physical activity is not only important for the prevention of microvascular diseases, but also contributes to the reduction in cardiac outcomes

post-diagnosis.

3.0 Study Rationale

A number of modifiable and non-modifiable factors impact the risk of traditional epicardial CAD. Previous research has shown that modifiable lifestyle factors, such as smoking, diabetes mellitus, hypertension, and hyperlipidemia (51), play a large role in the development of CMVD. However, much less is known about the interaction of these factors on the development and progression of microvascular dysfunction. As most individuals with microvascular dysfunction have "normal" looking arteries and do not have signs of arterial blockages, microvascular dysfunction is often seen as a relatively benign (52) condition that is often masked by traditional epicardial symptoms (51). However, it has recently come to light that those without visible CAD have an increased risk of adverse cardiac events (53), further emphasizing the importance of understanding the role of microvascular dysfunction in the development and progression of the disease.

The purpose of this study is to therefore to i) explore the relationship between early onset metabolic dysfunction (MetS and obesity) that may precede or co-occur and may be early warning signs for microvascular dysfunction, and; ii) examine the relationship between modifiable lifestyle-related risk factors (sleep, physical activity, and sitting time) and microvascular disease. Ultimately, this information aims to explore how individuals with microvascular dysfunction may differ in lifestyle factors from those who are diagnosed with more traditionally epicardial CAD. The following analyses will serve as a preliminary step to understanding the association between potential risk factors in microvascular dysfunction and its subsequent progression to debilitating cardiovascular conditions.

4.0 Objectives

The thesis aims to characterize the movement (PA) and non-movement (sedentary time, sleep) behaviors of patients with functional CAD, and see if it differs from the traditional CAD population.

Specific Aim 1: To examine the metabolic risk factors involved in patients with suspected CMVD in comparison to those with Epicardial disease.

Specific Aim 2: To describe patterns and examine existing associations between movement behaviour physical activity, sitting time, and sleeping patterns in patients with microvascular dysfunction.

Specific Aim 3: To estimate the odds of developing CMVD according to movement behaviour.

5.0 Methods

5.1 Participants and Data Collection

Data for this study is abstracted from the Advanced Coronary Physiology Program (ACPP) data registry at Southlake Regional Health Centre (SRHC) in Newmarket, Ontario. All patients referred to the physiology clinic at SRHC from January 2019 – March 2019 with possible CAD were eligible for the study. All patients provided verbal informed consent, and ethical approval was obtained from the Research Ethic Board at Southlake Regional Health Centre. Patient information was accessed through an anonymized dataset provided by the study PI and lead cardiologist, with geographic identifiers stripped to reduce the potential for residual disclosure.

Inclusion Criteria

Referrals for these patients were accepted from specialists throughout the region. A total of 594 patients were seen in the cardiology clinic, however 158 follow-up patients were excluded from the analysis (Figure 1) as this study focuses on initial consultations. A total of 436 patients were therefore included in the final analysis. SRHC referrals for patients with obstructive CAD were included to allow for a direct comparison of the similarities and differences of patients with suspected functional CAD for this thesis.

5.2 Study Variables

Dependent Variables

There are three outcome variables of interest in this study; CMVD, Epicardial and Unconfirmed referral groups. Both CMVD and Epicardial patients are classified based on baseline physician diagnosis.

Dependent Variables

Patient referral category were sorted into three diagnostic groups, functional CAD, epicardial CAD or 'Unconfirmed, based on a combination of medical history and clinical tests examined by the lead cardiologist at SRHC.

Independent Variables

Independent variables include i) self-reported questionnaires (socio- demographics, sleep quality and quantity, weight history, physical activity, sedentary time, attitudes towards exercise, and health-related quality of life); ii) anthropometric measures (body mass index (BMI: kg/m^2) and waist circumference (WC), and; iii) measures of blood chemistry (e.g. triglycerides, high-density lipoprotein cholesterol, and fasting blood glucose) necessary to identify the presence of MetS (Appendix A).

Metabolic Syndrome (MetS)

Metabolic syndrome is defined as having 3 out of 5 of the following characteristics: increased waist circumference (>102 cm [>40 in] for men, >88 cm [>35 in] for women), elevated triglycerides (≥150mg/dl), low HDL cholesterol (<40 mg/dl in men, <50 mg/dl in women), hypertension (≥130/ ≥ 85 mmHg), and impaired fasting glucose (≥100 mg/ dl) (NCEP ATP III) (29).

Sleep Quality

Sleep quality was assessed using the STOP-BANG questionnaire, a widely used screening tool for Obstructive Sleep Apnea. The STOP-BANG questionnaire (Appendix B) consists of 4 STOP questions related to perception of sleep quality and sleep-related behaviour, and 4 additional questions regarding patient sociodemographic characteristics that are known to increase risk of sleep apnea. Patients were subsequently classified as "low risk" if they answered

'yes' to less than 3 questions, "intermediate" if they answered 'yes' to 3-4 questions, and "high" OSA risk groups if they answered 'yes' to 5-8 questions on the STOP-BANG questionnaire.

Sleep Duration

Sleep duration criteria were informed by a recent study by Kwok et al. (2018) wherein there was a U-shaped relationship between sleep duration on cardiovascular events (54). Consequent to this, patients in the "low risk" category included those who self-reported sleeping 6-8 hours per night, whereas those in the "high risk" groups had less than 6 hours of sleep or more than 9 hours of sleep.

Physical Activity

As recommended by the Canadian Physical Activity Guidelines (Canadian Society for Exercise Physiology, 2012), individuals are deemed physically active if they accumulate more than 150 minutes of moderate to vigorous physical activity per week (55). Patients were asked during their visit with their cardiologist if they "perform at least 150 minutes of moderate physical activity per week." As a result, patients were deemed either physically inactive or active based upon the physical activity cut-offs.

Sedentary Time

Participants were asked "in a typical day, of your working hours, how much time do you spend sitting." Those who spent less than, and including, half their waking hours sitting were deemed non-sedentary. Those who answered that they spent more than half their waking hours sitting were categorized as "sedentary" (56).

Cardiac Syndrome X, Y

When possible, participants were classified as either suspected syndrome X or syndrome Y cases based on clinician diagnosis. These variables will be briefly examined due to emerging data that characterizes microvascular dysfunction amongst those with both cardiac syndrome X and cardiac syndrome Y (57, 42).

5.3 Statistical Analysis

Data are expressed as mean ± S.D for continuous variables and number and percentage for categorical variables. As not all participants answered the same questionnaires, pairwise deletion methods were employed in order to obtain maximize sample size. Comparisons between referral categories and continuous variables were completed using a one-way analysis of variance. Comparisons between categorical groups were performed using χ^2-tests for independence. Logistic regression was performed in three different models to investigate the relationship between BMI, sleep quality, physical activity, and sedentary behaviour on referral category. Model 1 is unadjusted, model 2 is adjusted for age- and sex-adjusted, and model 3 is adjusted for BMI, sex, age, sleep, exercise and sedentary behaviour. Odds ratios with 95% confidence intervals are presented. For all analyses, statistical significance was judged at an alpha level of 0.05. All statistical analyses were performed using SAS version 9.4 (Cary, NC).

6.0 Results

Baseline descriptive characteristics for participants are found in Table 1, classified by referral diagnosis. Overall, study participants are predominantly white (82.4%), married (71%) men (54.7%), with full-time employment (43.2%) at the time of first clinic visit. Almost half of participants (49.3%) had a history of smoking cigarettes and 41% reported daily alcohol consumption, whereas only 12.4% had ever used cannabis products. Notably, the frequency of males and females seems to be inversed in the Epicardial group when compared to the CMVD group; 60.1% of the CMVD population consists of females, whereas only 31.2% of Epicardial participants are female.

Table 2 shows the metabolic characteristics by referral category of study participants. CMVD patients tended to have a higher mean age (CMVD: 62.0 y vs Epicardial: 58.5 y). Overall, there were no observable differences found in anthropometric measures; mean BMI within all three referral groups were all close to 27 kg/m^2, implying that most patients were classified as overweight. Mean waist circumference and the prevalence of abdominal obesity was also similar between all three groups. Metabolic factors, such as mean fasting glucose and mean systolic and diastolic blood pressure, were also similar across referral groups, whereas the CMVD group had lower mean triglycerides (1.2 ± 0.6 mmol/L), HDL (1.4 ± 0.4 mmol/L) and LDL (1.5 ± 0.7 mmol/L) when compared to both Epicardial (1.6 ± 1.1 mmol/L, 1.5 ± 0.8 mmol/L, and 2.2 ± 0.9 mmol/L) and unconfirmed (1.5 ± 1.0 mmol/L, 1.4 ± 0.7 mmol/L, and 1.9 ± 0.9 mmol/L) categories. The majority of patients fell within the normal ranges for blood pressure at the time of examination, as only 11% of all patients had elevated blood pressure. Nonetheless, almost a quarter (24.8%) of all participants met the MetS criteria (>3 out of 5 risk factors), with a higher frequency found in those with CMVD (28%) when compared to

Epicardial (22%) and Unconfirmed (20%). In addition, 29% of CMVD participants had 'High' CRP levels compared to 18.1% of Epicardial patients, and 17.2% out of those that are Unconfirmed. This is to say that participants were divided almost equally amongst CRP level groups in those with CMVD, whereas the bulk of participants in both Epicardial and Unconfirmed groups were in low (50%) and intermediate (58.6%) CRP level groups, respectively.

Table 3 shows patient-reported health outcomes by referral category. According to patient reports, myocardial infarctions (MI) are the most prevalent amongst all three referral groups, with hypertension closely following (49%). Almost three quarters (74.1%) of the epicardial participants had reported a previous MI, in comparison to only 39.4% in those with CMVD. remains to be a recurring concern in almost half of the study population (49%). Significance was found in patients reporting a history of osteoarthritis (CMVD: 4.3% vs Epicardial: 3.5%), gastroesophageal (CMVD: 17.8% vs Epicardial: 9.4%) and anxiety (CMVD: 16.3 % vs Epicardial: 5.8%) concerns. In each case, CMVD patients had a higher frequency when compared to Epicardial and Unconfirmed groups.

Figure 2 illustrates CMVD subtypes, divided by syndrome X, syndrome Y, and other, by gender. Most participants are grouped within 'syndrome X' category (39.9%), with only 30.8% of participants are suspected syndrome Y participants, and 29.3% were grouped as 'Other.' Amongst CMVD patients, approximately 61.4% of Syndrome X patients are females, and 38.8% males. Comparatively, 64.0% of Syndrome Y participants are females, with males encompassing the remaining 36.0%.

In terms of movement behaviors, no difference in meeting PA guidelines across referral categories was observed (Table 4). CMVD: 51.8% of CMVD patients are meeting recommended guidelines, while 48.2% that are not. In contrast, 63.4% of Epicardial patients are meeting guidelines; the remaining 44.7% have stated that they do not complete 150 minutes of moderate exercise per week (Table 4). Sitting time and online screen time (Table 4) follow similar patterns in that very few clinic patients report sitting almost all of the day (4.4%), and approximately one-quarter (25.1%) of participants reported being on the computer for less than 2 hours per day. When examining risk of sleep apnea with the STOP-BANG criteria (Table 4), the majority of participants in all three referral groups were classified as either low or intermediate risk. Over one-quarter of epicardial patients were classified in the high-risk STOP-BANG group, closely followed by the CMVD group (24.9%) and the Unconfirmed group (24.1%). Interestingly, CMVD patients showed signs of poor sleep patterns, as there was almost double the number of CMVD patients that slept for less than 5 hours a night (20.2% vs Epicardial: 11.6%). These trends are seen again when assessing self-perceived sleep quality amongst referral groups, as less than half of the CMVD patients (40.9%) revealed that they woke up feeling more rested, in comparison to 57.3% of Epicardial patients that wake up feeling rested. A significant proportion of CMVS participants (77.7%) have reported feeling fatigued during the day, in contrast to only 59.8% of Epicardial patients and 53.1% of unconfirmed cases that report feeling fatigued.

Table 5 examines sitting time, physical activity, and sleep quality and quantity amongst CMVD-BMI groups. Amongst participants with CMVD and classified as under/normal weight, 77.6% report sitting for less than half the day, and 65.3% state that they are meeting minimum PA guidelines. Similarly, 73.9% of those in overweight groups along with 63.3% in obese groups have indicated that they sit for less than half the day, and approximately half of both

groups are meeting minimum exercise guidelines (50% and 43.3% respectively). Strikingly, 49.2% of participants of obese-CMVD groups are at high risk of sleep apnea, compared with only 3.8% of those in the under/normal weight groups.

Results of the logistic regression analysis in Table 6 demonstrate that when adjusted for all variables, those in the obese BMI category had 1.32 greater odds of suspected CMVD when compared to those in the underweight/normal groups. When adjusting for all confounding variables, those who reported feeling fatigued during the day had more than a twofold increase (OR: 2.27 [95% CI: 1.06- 4.88]) in odds of suspected CMVD than those who answered 'no' to the same question. Similarly, those who answered 'no' to feeling rested in the unadjusted group had a 37% increase in odds (OR: 1.37 [95% CI: 0.74 – 2.55]) of being classified as CMVD than those who answered 'yes.' Those in the higher risk, but not intermediate risk CRP level categories had a little over twice the odds (OR: 2.09 [95% CI: 1.05 – 4.14]) of being a suspected CMVD case than those in the lower risk CRP level group. Finally, despite trends for difference in CMVD at the descriptive level, no significance was discovered between sexes, regardless of adjustments.

7.0 Discussion

This study aimed to compare patterns of sociodemographic, medical, and health behavior factors between coronary epicardial and CMVD patients in a clinical setting. Specifically, this study explored potential differences in existing risk factors between diagnostic groups, many of which were modifiable in nature. Notably, sleep quality was found to differentiate CMVD, with non-significant findings for other movement and non-movement behaviors. Although distinct differences in the prevalence of obesity, inflammation, and MetS were not found, the overall patterns suggest the need for additional work.

CMVD Participant Profiles

Despite functional differences in the vasculature between CMVD and traditional CAD groups, CMVD participants patient profiles closely resembled those of epicardial patients. Patients in all three referral groups were predominantly white and married, although this may be a result of the overall demographic of the city hospital. Patients also had similar mean ages, around 60 years of age. In terms of anthropometrics, average BMI and WC were similar across groups (mean: 27.8 kg/m^2), signifying that a majority of the CAD population were classified as overweight. Previous larger studies, such as the Framingham Heart Study and the Nurses' Health Study (58, 59) have all identified increased rates of CAD-related mortality in individuals classified with overweight or obesity. Larger studies of the same caliber are less frequent with respects to CMVD, however a large meta-analysis of over 44,000 individuals found that an increased BMI was also associated with elevated risks of narrowed arteriolar and wider retinal venular caliber (29) ultimately leading to microvascular impairments. It is therefore not surprising that no changes were observed between both groups, considering that an elevated BMI have been proven risk factors for both obstructive CAD and CMVD alike.

Variation in CMVD Subtypes by Sex

Despite these similarities, the frequency of female CMVD patients when compared to those in both referral categories are worth mentioning. Consistent with previous literature (60), the majority of the CMVD sample is female (60.1%), whereas these proportions are almost reversed in both the epicardial and unconfirmed groups, with approximately one-third of their cohorts being female. As women with coronary microvascular dysfunction are often menopausal or approaching menopause when diagnosed with CMVD (61), hormonal differences are likely to play an important role. While research surrounding these differences is still in its infancy, a few pathophysiological theories suggest differences, such as decreased estrogen levels (62), which has been shown to have a strong protective effect on the development of cardiovascular diseases (63), and tends to favor factors that increase the ratio of vasodilation over vasoconstriction (64). It is therefore hypothesized that after menopause, there is a large decrease in estrogen levels amongst women, increasing their likelihood of developing coronary microvascular dysfunction (64). According to results from various cross-sectional studies, the median age at menopause for white women, similar to our cohort, is between 50 to 52 years of age (65). Despite this, the mean age difference between males and females with CMVD in our study do not vary greatly (~1.3 years in age).

In an effort to obtain a better representation of the CMVD patient demographics, our study sorted microvascular patients based on suspected syndrome X or syndrome Y characteristics. Many with microvascular dysfunction are oftentimes classified as "Syndrome X" cases; clinical features typically include angina with normal coronary arteries. "Syndrome Y", or "coronary slow flow phenomenon", possesses similar characteristics, except for the added dysfunction of elevated arterial resistance, as demonstrated by a slow progression of the dye

injected into the coronary vasculature upon coronary angiography (66). Both syndromes are most commonly associated with impaired microvascular function and are typically seen as subgroups of CMVD (67). This is seen in our findings, as both syndrome X and syndrome Y were significantly associated with the CMVD study participants. Our data has shown an almost equal divide between both suspected subgroups in CMVD participants, with no particular syndrome taking a lead. Additional differences are often seen on a population level between syndrome subgroups; those with syndrome X are more likely to be older menopausal women, whereas those with suspected syndrome Y have typically been younger male smokers (68). These trends were not seen in our data, considering the frequency of males vs females were almost identical between the groups, displaying no real difference between the overall general population of those with syndrome x and syndrome y within CMVD groups.

Risk Factors amongst All Referral Groups

Metabolic Factors

Consistent with previous literature (69), many metabolic risk factors, such as triglyceride levels, HDL, LDL levels and waist circumference were elevated in all coronary referral groups. Similarly, high rates of MetS were common in both macrovascular and microvascular patients in our study. Past research has also found that shared risk factors for both CMVD and traditional cardiovascular diseases include smoking, diabetes, age, hypertension, and hyperlipidemia (70). However, in the present analysis, waist circumference, and LDL levels were all higher in in CMVD patients, whereas triglycerides and HDL were all lower when compared to epicardial patients. Interestingly, recent literature suggests that systemic inflammation plays a large role in the development of coronary artery disease and may be an even larger risk factor in those with

CMVD (51). C-reactive protein (CRP), also found to have a significant association to coronary referral groups, is a traditional marker of inflammation that has been shown to be heavily tied to triglycerides, obesity, blood pressure, and fasting glucose (71). It is for this reason that CRP levels have been reported as being a reflective marker of cardiac health, as it encompasses many of the risk factors present in those with CAD. The presence of CRP is not only a marker of poor coronary health, but is indicative of reduced coronary flow, a hallmark adaptation of patients with CMVD.

Movement Behaviours

Sleep Quality and Quantity

When assessing our primary outcome variables, sleep quality and quantity were found to have significant associations with referral category in our analysis. To be more precise, it was observed that a little under a quarter of all CMVD participants were experiencing shorter sleep periods at night (<5 hours per night), which is almost double the amount of short sleepers as the epicardial or unconfirmed referral groups. More specifically, more than half of those with suspected CMVD answered that they did not wake up feeling rested, whereas the reverse can be said for those in the epicardial group, as almost 60% of them revealed that they did waking up feeling rested. To date, very few studies have examined the relationship between sleep and coronary microvascular dysfunction; however, in those that have one of the most common sleep disturbances, obstructive sleep apnea (OSA) - has been linked to increased levels of C-reactive protein levels, as well as elevated apnoea-hypopnoea index (AHI) values - of which both are related to decreased coronary flow reserve, ultimately impairing coronary microvasculature (72), leading to symptoms of coronary microvascular dysfunction. Some of the most common

complaints of those with OSA are that of fatigue, loud snoring, and choking (73). When observing the frequency at which our participants felt fatigued during the day, almost 78% of those in the CMVD group had answered 'yes' to the question, a striking difference between the two other referral groups (Epicardial: 59.8 % vs Unconfirmed: 53.1%). The results of the STOP-BANG questionnaire, a validated screening tool for OSA (74), did not show significance between the three groups. Approximately a quarter of both CMVD and Epicardial participants were both placed in the high-risk groups, whereas an additional 15% of epicardial and CMVD patients were classified as intermediate-risk.

Finally, results of the logistic regression analyses revealed that the most consistent differences found amongst CMVD patients were noticed in sleep quality. Participants that felt they were not well rested were almost 95% more likely to have a CMVD diagnosis in the unadjusted model. Additionally, participants that felt as though they were fatigued during the day were almost 2.4 times more likely to have coronary microvascular dysfunction than a traditional epicardial case in the same model. These numbers remained significant after adjustment for age and sex, but not in fully adjusted models. Increased risk of obstructive sleep apnea risk, which was measured using the STOP-BANG criteria, was also found to be more frequent amongst CMVD patients with obesity, confirming a substantial relationship between sleep quality and CMVD outcome.

Physical Activity

Interestingly, physical activity patterns did not materially differ across diagnostic groups, despite our initial hypothesis. More specifically, there were no significant differences between referral groups amongst those who did (vs did not) meet current physical activity guidelines,

regardless of statistical adjustment. This may be explained in part by the high level of inactivity observed in all groups, as supported by earlier studies suggesting few differences between physical activity trends and potential risk factors patients with CMVD and those with traditional, epicardial disease (71).

Movement behaviours amongst CMVD participants

When observing sleep and sedentary behaviour within CMVD patients exclusively, patients who were also classified as obese tended to have significantly worse sleep and activity patterns than those who were non-obese. Our analysis revealed significant associations between sitting time in participants with CMVD that were obese vs normal and overweight groups. Similarly, a notable association was found between obese and normal weight CMVD participants and STOP-BANG risk levels. Multiple studies have made obesity a key focus of CMVD (75, 76) as impaired microvascular dysfunction is commonly observed in individuals with (vs without) obesity (32). Although it is well understood that obesity is a significant risk factor in the development of CMVD, the exact role of obesity in CMVD functioning remains poorly understood. It has been proposed that some of the pathophysiological mechanisms through which obesity affects coronary microvascular dysfunction is through adipocyte-derived factors that contribute to vascular oxidative stress, increased neurohormonal activity as well as systemic inflammation (32). In line with this, our study confirmed a positive association between CRP, an acute inflammatory marker and both BMI and coronary microvascular dysfunction. As seen in our analysis, those with high risk CRP levels, when compared to low risk, are almost 2.5 times more likely of developing CMVD when compared to traditional epicardial patients. Additionally, patients classified as "obese" were 31.7% more likely to have CMVD when compared to those in

the normal BMI category.

7.1 Limitations

This study had several important limitations to note. The first limitation was that our participant pool was relatively homogenous, and participant data was collected upon initial visit. As a result, patient diagnoses are all "suspected" cases (of CMVD), which were undergoing further clinical investigation (and could change over follow-up). Furthermore, patients were sorted into referral categories based on a variety of symptoms and tests completed, which may vary from patient to patient. Preliminary diagnoses were a result of the cardiologist on site, and not through a standard test. This increases uncertainty and variability within our sample. Due to the uniqueness of this clinic sample and the exploratory nature of this work, a final analytic sample was not held constant through all analyses, and not all sections of the questionnaires were completed by each patient. Additionally, information on patient medications were not accounted for, which may ultimately impact on the interpretation of metabolic profile data. As this is a cross-sectional study, a significant limitation to consider is that of a lack of temporal evidence between exposure and outcome variables as they are studied and assessed at the same time. Lastly, because almost half of the data used in this study was self-reported, we cannot exclude the possibility of recall and healthy responder bias on the observed relationships.

7.2 Conclusion and Future Directions

It is important to note that despite differences in the risk factors found between CMVD and Epicardial patients, the majority of variables examined showed no overt difference between the referral groups. Further research, however, is necessary after definitive diagnosis and follow-

up, to either establish or refute the presence of movement behavior differences, as well as to examine longer-term outcomes (e.g. healthcare utilization, recurrent coronary events, and mortality).

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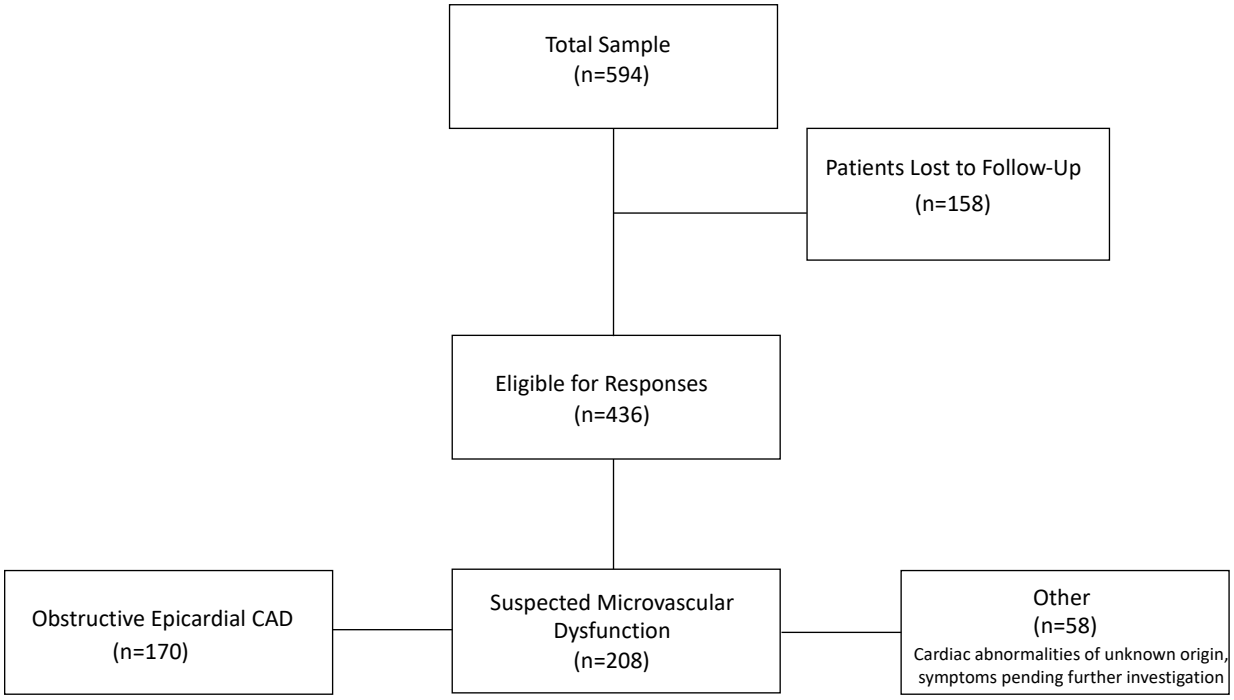

Figure 1: Flow Chart of final participant study size

Table 1: Frequency table of descriptive characteristics by referral category.

	CMVD	Epicardial	Unconfirmed	Total
Sex ***	*n=208*	*n=170*	*n=57*	*n=435*
Male	83 (39.9%)	117 (68.8%)	38 (66.7%)	238 (54.7%)
Female	125 (60.1%)	53 (31.2%)	19 (33.3%)	197 (45.3%)
Ethnicity *	*n=205*	*n=167*	*n=49*	*n=421*
White	175 (85.4%)	130 (77.8%)	42 (85.7%)	347 (82.4%)
South Asian	3 (1.5%)	13 (7.8%)	0 (0.0%)	16 (3.8%)
Asian	8 (3.9%)	13 (7.8%)	5 (10.2%)	26 (6.2%)
African-American	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Aboriginal	4 (2.0%)	1 (0.6%)	0 (0.0%)	5 (1.2%)
Other	14 (6.8%)	10 (6.0%)	2 (4.1%)	26 (6.2%)
Employment Status	*n=205*	*n=167*	*n=49*	*n=421*
Full Time	84 (41.0%)	77 (46.1%)	21 (42.9%)	182 (43.2%)
Part Time	13 (6.3%)	11 (6.6%)	2 (4.1%)	26 (6.2%)
Not Looking For Work	1 (0.5%)	4 (2.4%)	1 (2.0%)	6 (1.4%)
On Disability	32 (15.6%)	13 (7.8%)	6 (12.2%)	51 (12.1%)
Unemployed	7 (3.4%)	6 (3.6%)	1 (2.0%)	14 (3.3%)
Retired	62 (30.2%)	56 (33.5%)	18 (36.7%)	136 (32.3%)
Caregiver	6 (2.9%)	0 (0.0%)	0 (0.0%)	6 (1.4%)
Marital Status *	*n=205*	*n=167*	*n=49*	*n=421*
Married	138 (67.7%)	121 (72.5%)	40 (81.6%)	299 (71.0%)
Single	24 (11.7%)	22 (13.2%)	3 (6.1%)	49 (11.6%)
Divorced	6 (2.9%)	10 (6.0%)	2 (4.1%)	18 (4.3%)
Widow(er)	16 (7.8%)	7 (4.2%)	3 (6.1%)	26 (6.2%)
Domestic Partner	21 (10.2%)	7 (4.2%)	1 (2.0%)	29 (6.9%)
Smoking History	*n=204*	*n=167*	*n=49*	*n=420*
Current	23 (11.3%)	12 (7.2%)	4 (8.2%)	39 (9.3%)
Never	90 (44.1%)	64 (38.3%)	20 (40.8%)	174 (41.4%)
Previous smoker	91 (44.6%)	91 (54.5%)	25 (51.0%)	207 (49.3%)
Drinks per day	*n=204*	*n=167*	*n=49*	*n=420*
Never	74 (36.3%)	61 (36.5%)	20 (40.8%)	155 (36.9%)
Less than One	88 (43.1%)	66 (39.5%)	18 (36.7%)	172 (41.0%)
One	21 (10.3%)	26 (15.6%)	9 (18.4%)	56 (13.3%)
Two to Three	16 (7.8%)	12 (7.2%)	2 (4.1%)	30 (7.1%)
Three to Five	3 (1.5%)	2 (1.2%)	0 (0.0%)	5 (1.2%)
6 or more	2 (1.0%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
Cannabis Use	*n=204*	*n=167*	*n=49*	*n=420*
Never	183 (89.7%)	143 (85.6%)	42 (85.7%)	368 (87.6%)
Rarely	13 (6.4%)	9 (5.4%)	4 (8.2%)	26 (6.2%)
Regularly	2 (1.0%)	5 (3.0%)	2 (4.1%)	9 (2.1%)
Every week, not every day	5 (2.5%)	7 (4.2%)	0 (0.0%)	12 (2.9%)
Rather not say	1 (0.5%)	3 (1.8%)	1 (2.0%)	5 (1.2%)

Differences between the 3 groups were analyzed using χ^2. *P value for group differences <0.05. **p value for group differences <0.01 *** p value for differences <0.001

Table 2: Frequency of metabolic and clinical characteristics by suspected diagnosis.

	CMVD	**Epicardial**	**Unconfirmed**	**Total**
Age ($\bar{x} \pm SD$) *	*n=208*	*n=170*	*n=57*	*n=435*
Total	58.5 ± 14.5 [a]	62.0 ± 10.8	59.3 ± 14.6	60.1 ± 13.3
Male	59.3 ± 14.3 [ab]	61.5 ± 11.0	61.6 ± 14.2	60.8 ± 12.7
Female	58.0 ± 14.6 [ab]	63.2 ± 10.5	55.1 ± 14.7	59.1 ± 13.8
Anthropometric ($\bar{x} \pm SD$)	*n=207*	*n=170*	*n=57*	*n=434*
BMI (kg/m^2)	27.8 ± 5.5	28.6 ± 6.00	26.9 ± 5.4	28.0 ± 5.7
Underweight/Normal Weight	22.0 ± 3.5	22.3 ± 2.00	21.1 ± 4.9	22.0 ± 3.2
Overweight	27.5 ± 1.4	27.4 ± 1.4	27.2 ±1.5	27.4 ± 1.4
Obese	34.5 ± 3.6	35.5 ± 5.30	33.1 ± 3.4	34.8 ± 4.6
Waist Circumference (cm)	98.4 ±16.4	97.7 ± 18.7	92.8 ± 23.9	97.3 ± 18.7
High WC (>102 M, >88 F) *	106.6 ± 12.5 [a]	107.7 ± 10.7	99.0 ± 29.4	106.1 ± 15.1
MetS Risk Factors (%)	*n=149*	*n=118*	*n=30*	*n=297*
0	29 (19.5%)	24 (33.3%)	8 (2.7%)	61 (20.5%)
1	34 (22.8%)	31 (26.3%)	9 (30.0%)	74 (25.0%)
2	44 (29.5%)	37 (31.4%)	7 (23.3%)	88 (30.0%)
3	24 (16.1%)	24 (33.3%)	5 (16.7%)	53 (17.8%)
4+ **	17 (11.4%)	2 (1.7%)	1 (3.3%)	20 (6.7%)
5	1 (0.7%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Metabolic Factors ($\bar{x} \pm SD$)	*n=208*	*n=170*	*n=57*	*n=435*
Triglycerides *	1.2 ± 0.6 [a]	1.6 ± 1.1	1.5 ± 1.0	1.5 ± 1.0
HDL *	1.3 ± 0.4 [a]	1.5 ± 0.8	1.4 ± 0.7	1.4 ± 0.7
Fasting Glucose	5.9 ± 1.2	6.0 ± 1.9	5.9 ± 1.6	5.9 ± 1.6
Systolic Blood Pressure	122.2 ± 18.2	124.0 ± 17.7	123.1 ± 17.9	123.1 ± 17.9
Diastolic Blood Pressure	74.8 ± 10.7	76.1 ± 10.0	75.5 ± 10.4	75.5 ± 10.4
LDL ***	1.5 ± 0.7 [ab]	2.2 ± 0.9	1.9 ± 0.9	1.9 ± 0.9
CRP *	2.7 ± 3.3 [ab]	2.7 ± 6.0	2.0 ± 2.0	2.7 ± 6.0
Triglycerides	*n=155*	*n=125*	*n=34*	*n=314*
Levels > 2.2 mmol/L	25 (16.1%)	10 (29.4%)	5 (14.7%)	40 (12.7%)
HDL	*n=153*	n=124	*n=34*	*n=311*
M <1.04, F <1.29 mmol/L	43 (28.1%)	42 (33.9%)	8 (23.5%)	9 (2.9%)
Blood Pressure	*n=207*	*n=169*	*n=56*	*n=432*
≥ 130/85	25 (12.1%)	18 (8.7%)	5 (2.4%)	48 (11.0%)
< 130/85	182 (87.9%)	151 (91.3%)	51 (97.6%)	384 (88.3%)
Metabolic Syndrome	*n=149*	*n=118*	*n=30*	*n=297*
> 3 out of 5 criteria	42 (28.0%)	26 (22.0%)	6 (20.0%)	74 (24.9%)
< 3 out of 5 criteria	107 (72.0%)	92 (78.0%)	24 (80.0%)	223 (75.1%)
CRP Level **	*n=145*	*n=116*	*n=29*	*n=290*
Low < 1.0 mg/L	54 (37.2%)	58 (50%)	7 (24.1%)	119 (41.0%)
Intermediate 1.0 – 2.9 mg/L	49 (33.8%)	37 (32%)	17 (58.6%)	103 (35.5%)
High > 3.0 mg/L	42 (29.0%)	21 (18.1%)	5 (17.2%)	68 (23.5%)

Differences between groups: χ^2 for categorical variables, ANOVA for continuous variables. *P value for group differences <0.05. ** p <0.01 *** p <0.001.[a] significance between CMVD and epicardial group [ab] significance between all groups

Table 3: Frequency of patient-reported health outcomes by suspected diagnosis.

	CMVD	Epicardial	Unconfirmed	Total
Patient Reported Outcomes (%)	*n=208*	*n=170*	*n=57*	*n=435*
MI ***	82 (39.4%)	126 (74.1%)	34 (59.6%)	242 (55.6%)
CABG	1 (0.48%)	5 (2.9%)	0 (0.0%)	6 (1.4%)
AFIB	14 (6.7%)	11 (6.5%)	2 (3.5%)	27 (6.2%)
Clots	3 (1.4%)	4 (2.4%)	1 (1.8%)	8 (1.8%)
TIA	4 (1.9%)	2 (1.2%)	1 (1.8%)	7 (1.6%)
Claudication	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.2%)
FHPHD ***	79 (38.0%)	40 (23.5%)	7 (12.3%)	126 (29.0%)
Hypertension	108	83 (48.8%)	22 (39.0%)	213 (49.0%)
Diabetes	(51.9%)	42 (24.7%)	5 (8.8%)	79 (18.2%)
Hyperlipidemia	32 (15.4%)	77 (45.3%)	18 (31.6%)	193 (44.4%)
Psoriasis	98 (47.1%)	3 (1.2%)	1 (1.8%)	11 (2.5%)
Autoimmune	7 (3.4%)	2 (1.2%)	1 (1.8%)	11 (2.5%)
Osteoarthritis *	8 (3.8%)	6 (3.5%)	2 (3.5%)	28 (6.4%)
Gastroesophageal *	9 (4.3%)	16 (9.4%)	4 (7.0%)	57 (13.1%)
Anxiety **	37 (17.8%)	10 (5.8%)	5 (8.8%)	49 (11.3%)
MAD syndrome *	34 (16.3%)	19 (11.2%)	7 (12.3%)	71 (16.3%)
COPD	45 (21.6%)	4 (2.4%)	2 (3.5%)	19 (4.4%)
Cancer	13 (6.3%)	7 (4.1%)	3 (5.3%)	23 (5.3%)
Asthma	13 (6.3%)	8 (4.7%)	1 (1.8%)	24 (5.5%)
Liver	15 (7.2%)	3 (1.8%)	0 (0.0%)	6 (1.4%)
CFS	3 (1.4%)	0 (0.0%)	0 (0.0%)	3 (0.7%)
	3 (1.4%)			
Self-rated Health ($\bar{x}$ ± SD)		*n=18*	*n=2*	*n=82*
Physical QOL ***	*n=62*	3.0 ± 1.2	3.6 ± 0.7	3.6 ± 0.7
Psychological QOL *	3.5 ±1.1 [ab]	2.9 ± 1.0	3.3 ± 0.4	3.3 ± 0.4
	3.2± 1.0 [a]			

Differences between the 3 groups were analyzed using χ^2. *P value for group differences <0.05. **p value for group differences <0.01 *** p value for differences <0.001. [a] significance between CMVD and epicardial group. [ab] significance between CMVD group and 'Unconfirmed' group TG, triglycerides; BP, Blood Pressure; MI, Myocardial Ischemia; AFIB, Atrial Fibrillation, TIA, transient ischemic attack;

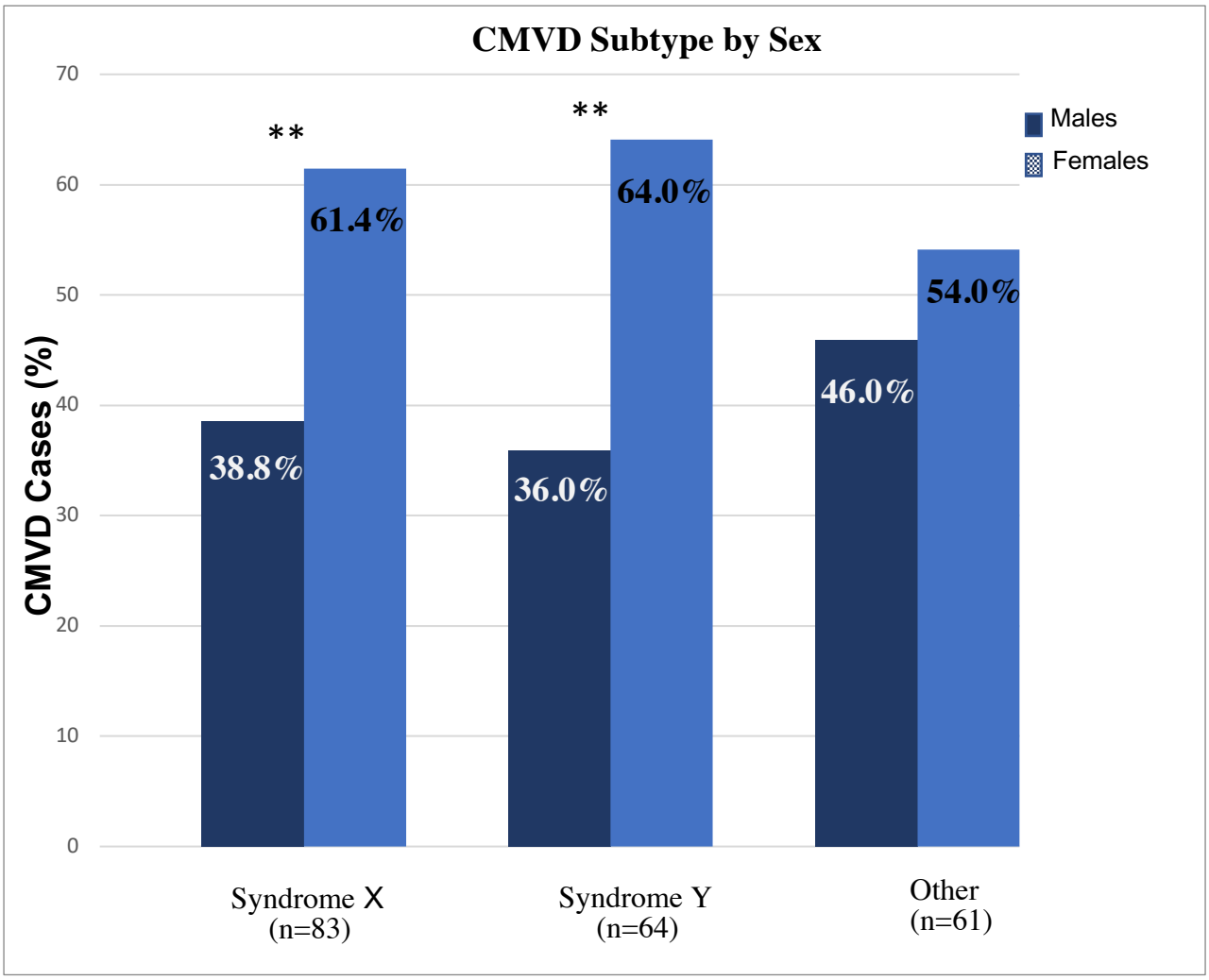

Figure 2: Bar graph of the number of CMVD (%) cases of syndrome x, syndrome y and 'other' by sex. Differences between the 3 groups were analyzed using χ^2.

Table 4: Frequency of movement behaviours by suspected diagnosis

	CMVD	**Epicardial**	**Unconfirmed**	**Total**
Physical Activity Level	*n=197*	*n=161*	*n=49*	*n=407*
Meeting Guidelines (≥ 150mins/week)	102 (51.8%)	89 (63.4%)	28 (57.1%)	219 (53.8%)
Not Meeting Guidelines (< 150mins/week)	95 (48.2%)	72 (44.7%)	21 (42.9%)	188 (46.2%)
Sitting Time	*n=197*	*n=161*	*n=49*	*n=407*
<1/4	47 (23.9%)	37 (23.0%)	10 (20.4%)	94 (23.1%)
1/4	41 (20.8%)	40 (24.8%)	16 (32.7%)	97 (23.8%)
1/2	53 (26.9%)	43 (26.7%)	16 (32.7%)	112 (27.5%)
3/4	45 (22.8%)	36 (22.4%)	5 (10.2%)	86 (21.1%)
Almost all day	11 (5.6%)	5 (3.1%)	2 (4.1%)	18 (4.4%)
Online Screen Time Per Day	*n=197*	*n=161*	*n=49*	*n=407*
<2	51 (25.9%)	37 (23.0%)	14 (28.6%)	102 (25.1%)
2	32 (16.2%)	27 (16.8%)	8 (16.3%)	67 (16.5%)
3	33 (16.8%)	31 (19.3%)	6 (12.2%)	70 (17.2%)
4	26 (13.2%)	19 (11.8%)	11 (22.4%)	56 (13.8%)
5	22 (11.2%)	13 (8.1%)	4 (8.2%)	39 (9.6%)
6+	33 (16.8%)	34 (21.1%)	6 (12.2%)	73 (17.9%)
STOP-BANG Score	*n=209*	*n=170*	*n=57*	*n=436*
Low Risk	77 (36.8%)	45 (26.5%)	24 (42.1%)	146 (33.5%)
Intermediate Risk	80 (38.3%)	81 (47.6%)	24 (42.1%)	185 (42.4%)
High Risk	52 (24.9%)	44 (25.9%)	9 (15.8%)	105 (24.1%)
Hours of sleep per night *	*n=203*	*n=164*	*n=49*	*n=416*
< 5	41 (20.2%)	19 (11.6%)	5 (10.2%)	65 (15.6%)
6	46 (22.7%)	53 (32.3%)	8 (16.3%)	107 (25.7%)
7	67 (33.0%)	63 (38.4%)	18 (36.7%)	148 (35.6%)
8	37 (18.2%)	23 (14.0%)	13 (26.5%)	73 (17.5%)
9+	12 (5.9%)	6 (3.7%)	5 (10.2%)	23 (5.5%)
Self-perceived Sleep Quality *	*n=203*	*n=164*	*n=49*	*n=416*
Wake up Rested **	83 (40.9%)	94 (57.3%)	22 (44.9%)	199 (47.8%)
Snore Loudly	69 (34.2%)	58 (35.4%)	13 (26.5%)	140 (33.7%)
Fatigued during day ***	157 (77.7%)	98 (59.8%)	26 (53.1%)	281 (67.7%)
Stop breathing during sleep	40 (19.8%)	36 (22.0%)	13 (26.5%)	89 (21.4%)

Differences between the 3 groups were analyzed using χ^2. *P value for group differences <0.05. **p value for group differences <0.01 *** p value for differences <0.00. PA, physical activity

Table 5: Frequency of sitting time, physical activity, and sleep quality and quantity amongst CMVD-BMI groups

	Under/Normal Weight	**Overweight**	**Obese**
Sitting Time [a]	n=49	n=88	n=60
Low Sitting Time (Less than 3/4 of day)	38 (77.6%)	65 (73.9%)	38 (63.3%)
Increased Sitting Time (3/4 of day or more)	11 (22.4%)	23 (26.1%)	22 (36.7%)
	n=49	n=88	n=60
Physical Activity Level	17 (34.7%)	44 (50.0%)	34 (56.7%)
< 150 mins MVPA	32 (65.3%)	44 (50.0%)	26 (43.3%)
≥ 150 mins MVPA	n=50	n=91	n=62
	20 (40.0%)	39 (42.9%)	28 (45.2%)
Hours of Sleep per night	30 (60.0%)	52 (57.1%)	34 (54.8%)
Inadequate Sleep (6 hours or less)			
Adequate Sleep (7 hours or more)			
	n=52	n=92	n=63 [a]
STOP-BANG Score [ab]	28 (54.0%)	36 (39.1%)	11 (17.5%)
Low Sleep Apnea Risk	22 (42.3%)	37 (40.2%)	21 (33.3%)
Intermediate Sleep Apnea Risk	2 (3.8%)	19 (20.7%)	31 (49.2%)
High Sleep Apnea Risk			

Differences between the 3 groups were analyzed using χ^2. *P value for group differences <0.05. [a] significance between group category and obese weight BMI group [b] significance between group category and normal weight BMI group

Table 6: Unadjusted and adjusted ORs movement behaviour variables by suspected diagnosis

Comorbidities	**Model 1**	**Model 2**	**Model 3**
BMI			
Overweight vs Underweight/Normal	1.20 (0.73 – 1.96)	1.58 (0.93 – 2.70)	0.62 (0.32 –1.18)
Obese vs Underweight/Normal *	1.32 (0.77 – 2.27)	1.62 (0.91 – 2.90)	0.28 (0.12 – 0.65)
MetS			
MetS vs No MetS	1.39 (0.79 – 2.44)	1.79 (0.98 – 3.28)	1.523 (0.77 – 3.03)
STOP-BANG			
Intermediate vs Low	0.58 (0.36 – 0.93)	0.95 (0.56 – 1.62)	14.90 (2.28 – 10.57)
High vs Low	0.69 (0.40 –1.19)	1.54 (0.82 – 2.90)	8.10 (2.54 – 25.91)
Exercise Guidelines (≥ 150mins/week)			
High Risk vs Low Risk	1.15 (0.76 – 1.75)	1.13 (0.73 - 1.76)	1.11 (0.63 – 1.96)
Sitting Time			
High Risk vs Low Risk	1.16 (0.73 – 1.86)	1.08 (0.66 – 1.78)	0.98 (0.59 – 1.66)
Sleep Quantity			
Ideal vs Poor	0.95 (0.63 – 1.44)	1.02 (0.66 – 1.58)	0.85 (0.48 – 1.50)
† **Self-perceived Sleep Quality**			
Not Rested *	1.94 (1.28 – 2.95)	1.47 (0.94 – 2.30)	1.37 (0.74 – 2.55)
Snore Loudly	0.95 (0.62 – 1.46)	1.20 (0.76 – 1.91)	1.81 (0.88 – 3.75)
Fatigued during day *	2.35 (1.49 – 3.70)	1.96 (1.21 – 3.17)	2.27 (1.06 – 4.88)
Stop breathing during	0.88 (0.53 – 1.46)	1.08 (0.63 – 1.84)	1.21 (0.52 – 2.79)
CRP Levels			
Intermediate vs Low Risk	1.48 (0.84 – 2.61)	1.38 (0.76 – 2.50)	1.38 (0.76 – 2.50)
High vs Low Risk *	2.36 (1.23 – 4.52)	2.07 (1.05 – 4.11)	2.09 (1.05 – 4.14)
Sex			
Female vs Male *	3.33 (2.17 – 5.10)	3.32 (2.16 – 5.11)	2.62 (1.32

*OR – Odds Ratio, CI – Confidence Interval. CMVD groups were used as reference group.
† Reference group include all those who answered "no."
Model 1: Unadjusted;
Model 2: Adjusted for age and sex;
Model 3: Adjusted for age, sex, BMI, STOP-BANG Score, Exercise, Sitting Time, Self-Perceived Sleep Quality, CRP levels.

Appendix A: Self-Reported Questionnaire

Name:

Date Of Birth

Sex: Male female other

Marital Status:

Single married domestic partner divorced widow(er)

Race:

African-American Asian Caucasian Native American South Asian other

Education:

Some education High school Some College/university College/University degree
Post graduate (ie masters or phd) professional (ie law, medicine)

Employment status:

Full time Part time retired unemployed on disability

Tobacco use?

I never smoked I currently smoke I smoked in the past but not now

If you currently smoke, how much do you smoke?:

Never rarely every week but not every day regularly but < 1 pack/day 1-2 packs per day >2 packs/day

How many alcoholic beverages do you consume per day (on average)

Never less than one one 2-3 3-5 6 or more

How often do you consume or smoke marijuana products

Never rarely every week but not every day regularly I'd rather not say

Morgen Sleep Questionaire

How many hours of sleep do you usually get per 24 hour period (ie every day)?
5 hrs or less 6 hours7 hours8hours 9hrs or more

When you wake up in the morning, do you usually rise feeling rested?
Yes no

STOP score

1. Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?

Yes no

2. Do you often feel tired, fatigued or sleep during the daytime?

Yes no

3. Has anyone observed you stop breathing during your sleep?

Yes no

4. Do you have or are you being treated for high blood pressure

Yes no

(Score /4)

*note "BANG" part of score will be done by NP
BANG components = BMI >35, Age >50, Neck circumference > 40 cm, Gender = male

Hi risk 5-7, intermediate risk 3-4

Restless Legs Syndrome Screen:

Do you have, or have you had recurrent uncomfortable feelings or sensations in your legs while you are sitting or lying down

Yes no

Do you, or have you had, a recurrent need or urge to move your legs while you were sitting or lying down?

Yes no

Score: /2

Anxiety Questionaire:
For the following questions, please answer on a scale of 0-4 with 0 = never to 4 = always

Do you feel tensed up?
0 (never) 1 2 3 4 (always)
Do you worry a lot?
0 1 2 3 4
Do you have panic attacks?
0 1 2 3 4
Do you feel something awful is about to happen?
0 1 2 3 4

Score: /16

Depression Questionaire:
For the following questions please answer on a scale of 0-4 with 0= always and 4 = never
** please note that the scale is reversed compared to above**

Do you take as much interest in things as you used to?
0 (always) 1 2 3 4(never)
Do you laugh as readily?
0 (always) 1 2 3 4(never)
Do you feel cheerful?
0 (always) 1 2 3 4(never)
Do you feel generally optimistic about the future?
0 (always) 1 2 3 4(never)

Score : /16

Physical Activity:

Vigorous Exercise:
Vigorous activities cause large increased in breathing or heart rate.
Examples include jogging aerobics, heavy yard work etc.

How many times per week do you do these vigorous activities for at least 10 minutes at a time?

0 1 2 3 4 5 6 7

On days when you do vigorous activities, how much total time per day do you spend on these activities?

10 minutes 20 minutes 30 minutes 40 minutes 50 minutes 60 minutes or more

Database Variable = # times per week x time spent

Per week do you perform at least 75 minutes of vigorous activity? Yes no

Moderate Exercise:
Moderate activities cause small increases in breathing or heart rate.
Examples include brisk walking, bicycling, vacuuming gardening etc.

How many times per week do you do these moderate activities for at least 10 minutes at a time?

0 1 2 3 4 5 6 7

On days when you do moderate intensity activities, how much total time per day do you spend on these activities?

10 minutes 20 minutes 30 minutes 40 minutes 50 minutes 60 minutes or more

Database variable = # times per week X time spent

Per week do you perform at least 150 minutes of moderate activity? Yes no

Database variable = vigorous + moderate exercise time

Sedentary Time:
In a typical day, of your waking hours, including work, how much time do you spend sitting?

Less than ¼ ¼ ½ ¾ almost all

In a typical day, how many hours do you spend on the computer and/or playing video games and/or watching television and/or reading:

< 2hrs 2 hours3 hours4 hours 5 hours 6hrs or more

Attitudes towards exercise and cardiac rehab:

You may be prescribed cardiac rehabilitation, including an exercise program, for your cardiac problem

For the next series of questions, circle a number from 1 to 7.
1- Very Strongly Disagree 2- Strongly Disagree 3. Disagree
4- Neither agree nor disagree 5 – Agree 6. Strongly agree
7 – Very Strongly Agree

1. My recovery may be hindered if I do not complete exercise-based cardiac rehab
2. In order to prevent more heart problems, exercise-based cardiac rehab is essential
3. The way to prevent my heart problem from worsening is to follow my exercise-based rehab program
4. A successful and lasting recovery may not be possible if I do not complete my exercise-based cardiac rehab.

5. I make it more likely to have recurrent heart problems if I do not complete exercise-based cardiac rehab.

6. The exercise-based cardiac rehab program designed for me will ensure my recovery
7. Completion of my exercise-based cardiac rehab will make me live longer
8. Following the advice the I have been given will have a very large impact on how quickly I recover
9. I have absolute faith in the effectiveness of the exercise-based rehab program

10. I am capable of completing all aspects of my exercise-based cardiac rehab program
11. I consider myself able to stick to my exercise-based rehab program even if it includes activities that I do not enjoy
12. I will have no serious difficulty in following the instructions of my exercise-bsaed rehab program
13. I believe that I will stick with my exercise-based rehab program

14. As medical conditions go, mine is serious
15. I see my cardiac problem as a serious threat to my quality of life
16. I fear that my cardiac problem with affect my long-term health
17. My cardiac problem is too serious to not follow medical advice

Susceptibility score: add Q's 1-5
Severity score: add Q's 14-17
Self-efficacy; Add Q's 10-13
Treatment efficacy: Add Q's 6-9

Quality of Life: SF-12 Questionnaire

1. In general would you way your health is:

excellent very good good fair poor

2. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

a) Moderate activities such as moving a table, pushing a vacuum cleaner, bowling or playing golf:

Yes limited a lot yes limited a little no not limited at all

b) climbing several flights of stairs

Yes limited a lot yes limited a little no not limited at all

3. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health

a) accomplished less than you would like
yes no

b) were limited in the kind of work or other activities
yes no

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of emotional problem (such as feeling depressed or anxious)?

a) accomplished less than you would like
yes no

b) didn't do work or other activities as carefully as usual
yes no

5. During the past 4 weeks, how much did pain interfere with your normal work ?

Not at all a little bit moderately quite a bit extremely

These questions are about how you felt and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks:

a) have you felt calm and peaceful?

all of the time, most of the time, a good bit of the time, some of the time, a little bit of the time, none of the time

b) did you have a lot of energy?

all of the time, most of the time, a good bit of the time, some of the time, a little bit of the time, none of the time

c) have you felt downhearted and blue?

all of the time, most of the time, a good bit of the time, some of the time, a little bit of the time, none of the time

During the past 4 week,s how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends relatives etc)

All of the time, most of the time, some of the time, a little bit of the time, none of the time

Symptomatic hormonal changes:

For Women:

Do you have regular periods: Y/N
If the answer is no, have you had a period in the past year: Y/N

Have you noticed any of the following:
Weight gain : Y/N
Hot flashes: Y/N
Night sweats: Y/N
Vaginal drynesss: Y/N
Joint pain: Y/N
Fatigue: Y/N
Memory problems: Y/N
Mood swings: Y/N
Urinary tract infections: Y/N
Decreased libido (sex drive) : Y/N
Score : /10

For Men:
Have you notice any of the following:
Weight gain: Y/N
Difficulty building muscle mass: Y/N
Erectile dysfunction: Y/N
Joint pain: Y/N
Fatigue: Y/N
Memory problems: Y/N
Mood swings: Y/N
Decreased libido (sex drive) : Y/N
Score: /9

Weight history:
What is your current weight?
What was your weight one year ago?
What was your weight at age 25?
What is the most that you have weighed?

Appendix B: STOP-BANG Questionnaire (49)

1. Snoring: Do you snore loudly (loud enough to be heard through closed doors)?
Yes No
2. Tired: Do you often feel tired, fatigued, or sleepy during daytime?
Yes No
3. Observed: Has anyone observed you stop breathing during your sleep?
Yes No
4. Blood pressure: Do you have or are you being treated for high blood pressure?
Yes No
5. BMI: BMI more than 35 kg m^{-2}?
Yes No
6. Age: Age over 50 yr old?
Yes No
7. Neck circumference: Neck circumference >40 cm?
Yes No
8. Gender: Male?
Yes No